Title page

Title: Audiologic phenotype of osteogenesis imperfecta: use in clinical differentiation

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Acknowledgements: The authors would like to express their gratitude to the participating Belgian, Dutch and Italian patients. FS holds a Ph.D. fellowship of the Research Foundation Flanders (FWO Vlaanderen), Belgium.

Abstract

Objectives: To describe the audiologic phenotype in osteogenesis imperfecta (OI).

Study design: Observational study.

Setting: Tertiary referral center.

Patients: One hundred eighty-two patients with genetically confirmed OI, aged 3 to 89 years.

Intervention: Diagnostic hearing evaluation through otoadmittance and acoustic stapedius reflex measurements, pure tone, and speech audiometry.

Main outcome measure(s): Prevalence, type, severity, symmetry, and audiometric configuration of the hearing loss in OI. Progression of hearing thresholds was determined by constructing age-related typical audiograms.

Results: Approximately 52.2% of all OI patients demonstrated hearing loss unilaterally (7.7%) or bilaterally (44.5%). Pure conductive, mixed and pure sensorineural hearing losses were observed in 8.5%, 37.8% and 11.6% of OI ears, respectively. Multiple linear regression revealed that thresholds progressed by 0.5 dB/year at 0.25 kHz to 0.8 dB/year at 0.8 kHz in the ears with conductive or mixed hearing loss. Pure sensorineural hearing loss progressed by less than 0.1 dB/year at 0.25 kHz to 1.2 dB/year at 8.0 kHz. Audiometric configuration was predominantly flat (70.5%) in the ears with conductive/mixed loss, and sloping (50.0%) in those with pure sensorineural loss.

Conclusions: Patients with OI are at risk for hearing loss. The hearing loss in OI may initiate at a young age and is progressive. However, the rate of progression, as well as the hearing loss severity, onset and configuration depend on the type of hearing loss, which may be conductive/mixed or pure sensorineural. For both types, age-related threshold audiograms are constructed and may help the clinician to estimate the course of the hearing loss in patients with OI. In addition, they may be valuable to distinguish between hearing loss associated with OI and other similar forms of hearing loss, such as in otosclerosis.

Key words: Osteogenesis imperfecta; hearing loss; age-related typical audiogram.

1. Introduction

Osteogenesis imperfecta (OI) is a rare generalized connective tissue disorder caused by a heterozygous mutation in the gene *COL1A1* or *COL1A2*. Both genes encode for type I (pro)collagen, an important protein in the extracellular matrix of bone, skin, sclerae, blood vessels, and tendons. The disease is clinically characterized by a high rate of bone fractures, which may occur spontaneously or after minor trauma, by blue sclerae, abnormal dentine, and hearing loss.

Sillence et al.[1] proposed a classification in which a mild (Type I), a lethal (Type II), a severe (Type III) and a moderate-to-severe (Type IV) phenotype are distinguished. The disease is inherited in an autosomal dominant manner, but, recently, identification of mutations in other, autosomal recessive, genes has resulted in addition of Types V to XI[2-4]. These novel types count for only 5% of all OI patients and have not been associated with hearing loss up to now[2], while about half of the OI patients with mutations in *COL1A1* and *COL1A2* are hearing impaired[5-12]. In adolescence or young adulthood, most often, a conductive hearing loss develops. It may be attributed to an otosclerosis-like focus of abnormal bone remodeling affecting the oval window region and causing stapes footplate fixation. In comparison with otosclerosis, the hearing loss in OI is characterized by an earlier onset and more often progresses to a mixed hearing loss in which the pericochlear involvement is more severe and extensive[5-12]. Stapes surgery has been proven to be an efficient technique to reduce the conductive component of the hearing loss in OI[13-17]. Thickened, irregular and hard footplates as well as brittle and soft footplates have been described. In addition, stapes crura may be atrophic or fractured. Postmortem histopathological examination of the temporal bones originating from a number of adult OI patients who had developed mixed hearing loss confirmed the presence of vascular and otosclerotic changes encroaching on the stapes footplate and entailing stapes ankylosis, which could involve cochlear and vestibular parts of the otic capsule as well[18-21]. Furthermore, thinning of the cortical layers of the otic capsule and the ossicles were observed. The ossicles may show marked porosity and fractures, and may contain an extensive number of spaces for vessels and soft tissue.

In a minority of the OI patients, a pure sensorineural hearing loss develops.

Hearing loss of either type is progressive in OI, but rarely ends up in total deafness[5, 8, 10]. In case of severe bilateral hearing loss with a substantial sensorineural component, cochlear implantation may offer a last solution. Though, patients should be well selected and inner ear architecture well evaluated preoperatively as the disease implies a higher risk on complicated electrode insertion and on

unwanted secondary stimulation effects. The latter is possibly due to reduced impedance to current spread in abnormal bone tissue[22-24].

In an attempt to link the hearing loss to the underlying OI genotype, no correlation was found between the development or the type of hearing loss and the mutated gene, being *COL1A1* or *COL1A2*, or the type of the mutation[25].

On the basis of an extensive audiometric examination in a large cohort of OI patients, the audiologic phenotype of the hearing loss associated with OI is presented. Age-related thresholds audiograms (ARTAs) are constructed to visualize the progression of hearing loss in OI and to provide age-related reference thresholds, which may be useful for clinicians concerned with this disease. Determination of ARTAs in OI has, to our knowledge, never been attempted before, probably because the underlying OI genotype was not systematically investigated in all patients.

2. Methods

2.1. Subjects

In a large study investigating a correlation between OI-related hearing loss and the underlying OI genotype, a cohort of Belgian, Dutch and Italian OI patients underwent audiologic evaluation at the departments of otorhinolaryngology from the Ghent University Hospital, the Radboud University Nijmegen Medical Center and at the pediatric department of the La Sapienza University of Rome. After exclusion of the patients with suspicion of hearing loss due to causes other than OI, such as otitis media and noise exposure, audiometric characteristics from 182 OI subjects (84 Belgian; 67 Dutch; 31 Italian) or 364 ears were analyzed. In case of previous middle ear surgery or cochlear implantation, the preoperative audiometric data were retrieved and included for analysis. The mean age of the patients (88 males; 94 females) at audiometric evaluation was 30.2 years (SD: 16.9; range: 3-89 years).

All subjects were identified with a mutation in either the *COL1A1* (n=149) or the *COL1A2* (n=33) gene and were clinically diagnosed as OI Type I (n=152), Type III (n=4) or Type IV (n=26).

2.2. Micro-otoscopy and audiologic evaluation

After micro-otoscopic examination of the ear by an experienced otologist, hearing was evaluated through otoadmittance and acoustic stapedius reflex (ASR) measurements, as well as pure tone and speech audiometry.

2.2.1. Otoadmittance and ASR measurements

Tympanograms and two-component admittance measurements were obtained bilaterally using an 85-dB SPL 226- and 678-Hz probe tone, respectively, and ipsi- and contralateral ASR thresholds were determined for 0.5, 1.0, 2.0 kHz, and broadband noise stimuli (TympStar, Grason Stadler Inc., MN, USA). The 678-Hz probe tone was not used in the evaluation of the Italian patients. Tympanograms at 226 Hz were classified according to types (A, A_s, A_d, B, and C) as described by Jerger[26]. The criteria elaborated by Vanhuyse et al.[27] were applied to classify 678 two-components admittance tympanograms into ears at resonance, mass controlled and stiffness controlled ears, and to decide whether they deviated from normal.

2.2.2. Pure-tone audiometry

Pure-tone and speech audiometry were performed in a double-walled sound-attenuated room. Applying the modified Hughson-Westlake method, air conduction (AC) thresholds were bilaterally determined at octave frequencies of 0.25 to 8.0 kHz and at half-octave frequencies of 3.0 and 6.0 kHz, as well as bone conduction (BC) thresholds at octave-frequencies of 0.25 to 4.0 kHz and half-octave frequency 3.0 kHz (AC 40 Clinical Audiometer, Interacoustics, Assens, Denmark). Masking noise was presented at the contralateral ear through a headphone to assess masked AC and BC thresholds according to Hood's plateau method, when interaural differences in AC or intra-aural air-bone gap (ABG) were beyond 40 and 10 dB, respectively. Pure tone average (PTA) was calculated for AC and BC on the basis of the thresholds at 0.5, 1.0 and 2.0 kHz.

Hearing loss was classified as (1) conductive: PTA (BC) < 15 dB HL and ABG ≥ 15 dB averaged over 0.5, 1.0 and 2.0 kHz; (2) pure sensorineural: PTA (AC) ≥ 15 dB HL and ABG < 15 dB averaged over 0.5, 1.0 and 2.0 kHz; (3) high-frequency sensorineural: AC thresholds > 30 dB HL averaged over 4.0, 6.0 and 8.0 kHz; and (4) mixed: PTA (BC) ≥ 15 dB HL and ABG ≥ 15 dB averaged over 0.5, 1.0 and

2.0 kHz. Hearing loss was substantiated by comparison with the 95th percentile value for gender- and age-related hearing thresholds[28].

The severity of the hearing loss was established as mild [15 dB HL ≤ PTA (AC) < 40 dB HL], moderate [40 dB HL ≤ PTA (AC) < 70 dB HL], severe [70 dB HL ≤ PTA (AC) < 95 dB HL] or profound [95 dB HL ≤ PTA (AC)] hearing loss. Audiometric configuration was determined, and according to Schlaugh & Nelson[29], classified into flat, gradually falling (5 to 12 dB rise or fall per octave), sharply falling (15 to 20 dB increase per octave), precipitously falling (flat or gradually sloping, then threshold increase of 25 dB or more per octave), peaked or saucer (20 dB or greater loss at the extreme frequencies but not at 1.0 and 2.0 kHz), trough (20 dB or greater loss at 1.0 and 2.0 kHz, but not at the extreme frequencies) or notched (20 dB or greater loss at one frequency with complete recovery at the adjacent frequencies) audiograms.

Asymmetric hearing loss was defined as more than 10 dB difference between the ears for at least two frequencies with a difference in PTA between the ears of more than 20 dB.

2.2.3. Speech audiometry

Speech audiometry was performed in all Dutch and Belgian patients over 5 years of age (n=114). A Dutch monosyllabic wordlist was presented monaurally under headphone with contralateral masking noise if appropriate to determine the speech reception threshold (SRT) and the maximal perception percentage.

2.3. Statistical analysis

All mathematical computations and statistical processing were performed using SPSS, software version 15.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of quantitative variables was evaluated by the Kolmogorov-Smirnov test. In the group of patients with hearing loss, progression of the hearing impairment was analyzed at each frequency by multiple linear regression analysis, with age, sex, and mutated gene (*COL1A1* or *COL1A2*) as independent variables and the hearing threshold as outcome variable. At each frequency, different regression equations were obtained for AC and BC. The regression coëfficient for age represents the frequency-specific annual threshold deterioration (ATD) expressed in decibels per year. Hence, ARTAs at ages 10, 20, 30, 40, 50, and 60 years were constructed.

3. Results

3.1. Micro-otoscopic examination

Micro-otoscopy revealed normal eardrums in 52.2% of all the evaluated OI ears (N=364). Translucent eardrums were found in 42.3% of OI ears and 5.5% exhibited signs of atrophic scarring or tympanosclerosis.

3.2. Audiometric evaluation

3.2.1. Prevalence and type of hearing loss

In 52.2% of the OI patients hearing was impaired unilaterally (7.7%) or bilaterally (44.5%), providing a 47.8% prevalence of hearing impairment in the total number of 364 OI ears. The different types of hearing loss diagnosed in these ears are summarized in Table 1. A mixed hearing loss was the most frequently observed hearing loss type. In five ears with total deafness, retrieval of audiometric history revealed that mixed hearing loss had preceded the deafness in all cases.

Table 1. Prevalence and types of hearing loss in 364 osteogenesis imperfecta ears.

Hearing phenotype	**No. of ears (%)**	
Normal hearing	190	(52.2)
Pure conductive hearing loss	31	(8.5)
Mixed hearing loss	96	(26.4)
Pure sensorineural hearing loss	37	(10.2)
High-frequency sensorineural hearing loss	5	(1.4)
Deafness	5	(1.4)

In Figure 1 the prevalence and types of hearing loss are presented as a function of age, the latter classified into seven distinct age categories. The ears presenting total deafness and the ears with high-frequency sensorineural hearing loss were included in the groups of mixed and pure sensorineural hearing loss, respectively. Pure conductive loss was present in a minority of patients, all from the younger age groups, whereas mixed and pure sensorineural losses were observed more frequently and at all ages. The proportion of patients with hearing impairment increased till the fourth decade, after which it remained relatively stable. Our male and female OI population did not differ in the prevalence or type of hearing loss.

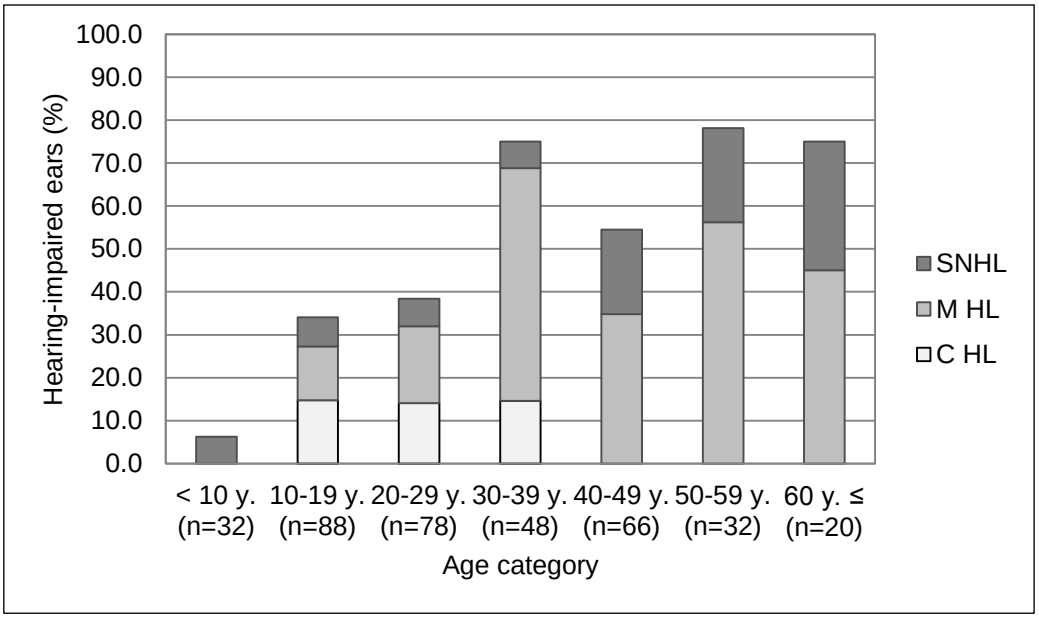

Figure 1 Prevalence and type of hearing loss in different age categories of patients with osteogenesis imperfecta.
The vertical bars represent the percentage of hearing impaired ears in seven different age categories of patients with osteogenesis imperfecta. A color code is applied for distinction between conductive (C HL), mixed (M HL) and pure sensorineural hearing loss (SNHL).

3.2.2. Hearing loss onset

In the analysis of the subjective onset of the hearing loss in OI, the pure conductive and mixed hearing losses were pooled because conductive hearing loss in OI usually evolves to a mixed hearing loss with time and an identical underlying pathology is assumed. The onset of conductive/mixed hearing loss was mainly situated in the second to fourth decades of life with a mean age at onset of 21.3 years (SD: 9.7; range: 5-42 years). Pure sensorineural hearing loss was reported to have developed at any age with a mean onset age of 30.2 years (SD: 14.3; range: 10-50 years).

3.2.3. *Severity of hearing loss*

The hearing loss severity varied with age and with the type of hearing loss. Pure sensorineural losses were mainly (95.2%) mild (15-40 dB HL), and in a few cases (4.8%), moderate (40-75 dB HL). The conductive/mixed hearing losses were mild to moderate in the younger age groups and varied from mild to profound (>95 dB HL) in the age categories above 40 years of age. However, one ear in the age category 10 to 19 years showed a severe mixed hearing loss.

3.2.4. Audiometric configuration

Most of the conductive/mixed hearing losses were characterized by a flat audiogram (70.5%), followed by gradually falling (16.6%), precipitously falling (9.1%), rising (2.3%) and sharply falling audiograms (1.5%). Pure sensorineural losses most often showed a sloping audiogram (50.0%), which was precipitously falling in 33.3% and gradually falling in 16.7%. Still, a considerable part of sensorineural losses had a flat audiogram (45.2%). One patient with pure sensorineural hearing loss demonstrated an atypical trough audiogram bilaterally.

3.2.5. Symmetry of hearing loss

All patients demonstrating bilateral hearing loss had identical hearing loss types in both ears, except 6 patients who demonstrated a conductive or mixed hearing loss in the one, and a pure sensorineural hearing loss in the other ear. Furthermore, 8 and 6 patients showed unilateral conductive or mixed and unilateral pure sensorineural hearing loss, respectively. In 17.3% of the patients with bilateral hearing loss, the recorded audiograms for left and right ears were asymmetric.

3.2.6. ARTA

Mutiple linear regression was carried out on each frequency to construct ARTAs at ages 10, 20, 30, 40, 50 and 60 years for conductive evolving to mixed hearing loss and for pure sensorineural hearing loss, separately. The analysis revealed no effect of the mutated gene on the progression of the hearing thresholds in patients with conductive/mixed hearing loss nor in those with pure sensorineural loss, enabling us to join patients with *COL1A1* and *COL1A2* mutations together in further calculations. In contrast, sex significantly ($P<0.05$) determined the progression of the thresholds in the instance of pure sensorineural hearing loss but not in the conductive/mixed hearing losses. Therefore, distinct ARTAs are created for female and male patients with pure sensorineural loss. Figure 2 displays the ARTAs for AC and BC for OI patients developing hearing loss characterized by a conductive component. Linear regression on the ABG revealed no dependency of age at any frequency. One-way analysis of variance with frequency as independent variable and ABG as outcome variable yielded that ABG was frequency-specific ($P<0.001$) exhibiting the largest values at the lowest frequencies. The hearing loss is progressive at all frequencies, with an ATD averaged over the frequencies 0.5, 1.0, and 2.0 kHz of 0.6 dB/year for AC and 0.4 dB/year for BC, respectively. ATD is most prominent at the

highest frequencies, attaining 0.9 dB/year and 0.8 dB/year for AC thresholds at 4.0 and 8.0 kHz, respectively.

The ARTAs reflecting the AC thresholds in male and female OI patients with pure sensorineural loss are given in Figure 3. The average ATD over the frequencies 0.5, 1.0, and 2.0 kHz was 0.2 dB/year, whereas at 4.0 and 8.0 kHz the ATD mounted to 0.9 dB/year and 1.2 dB/year, respectively.

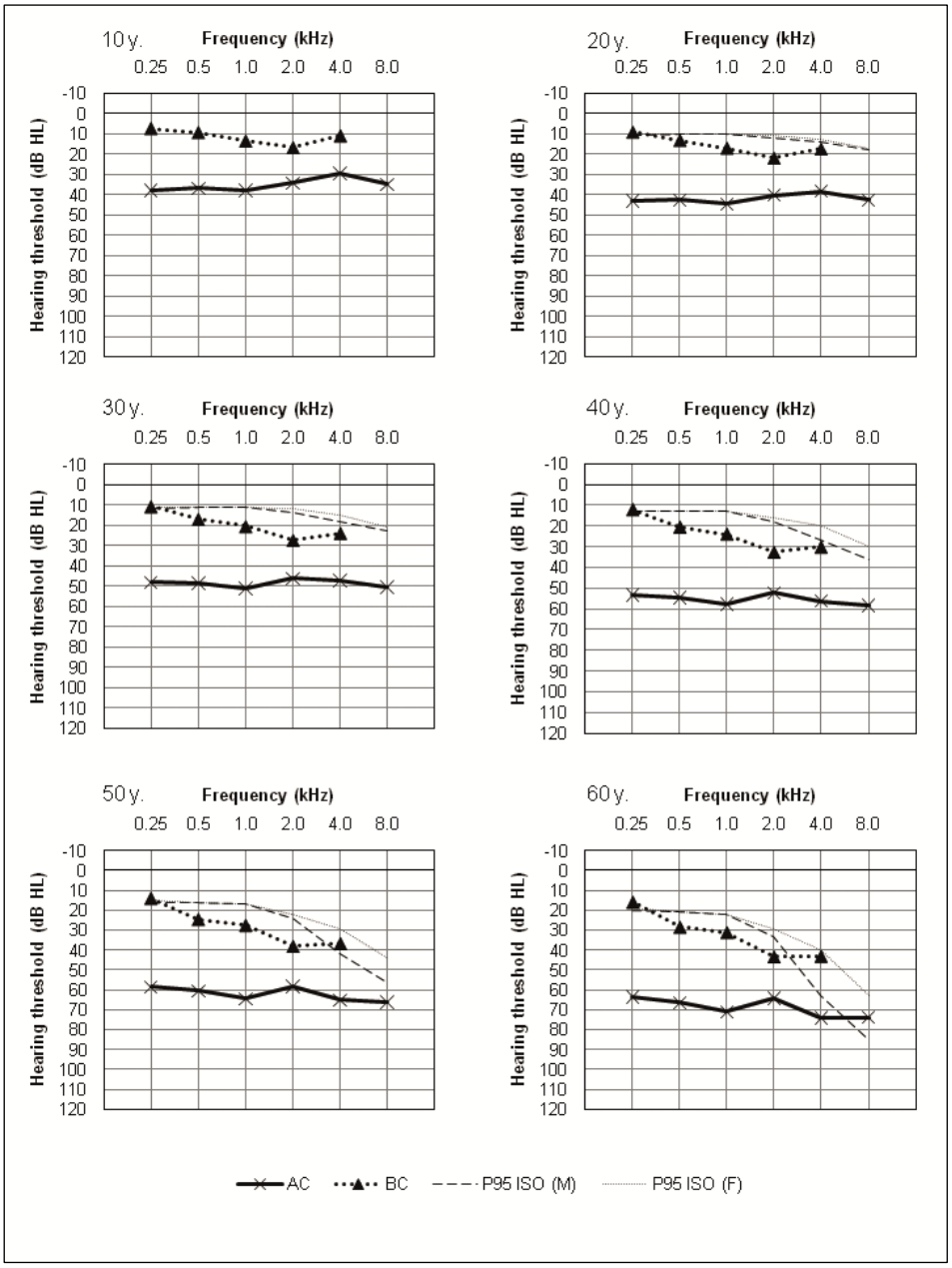

Figure 2. Age-related thresholds audiograms for osteogenesis imperfecta patients developing conductive/mixed hearing loss

Six different audiograms represent the average audiometric air conduction (AC) and bone conduction (BC) thresholds of patients with osteogenesis imperfecta developing hearing loss of the conductive/mixed type at ages 10, 20, 30, 40, 50, and 60 years. Age-related air conduction thresholds corresponding to the 95th percentile in the healthy adult female [P95 ISO (F)] and male [P95 ISO (M)] population are indicated on the audiograms.

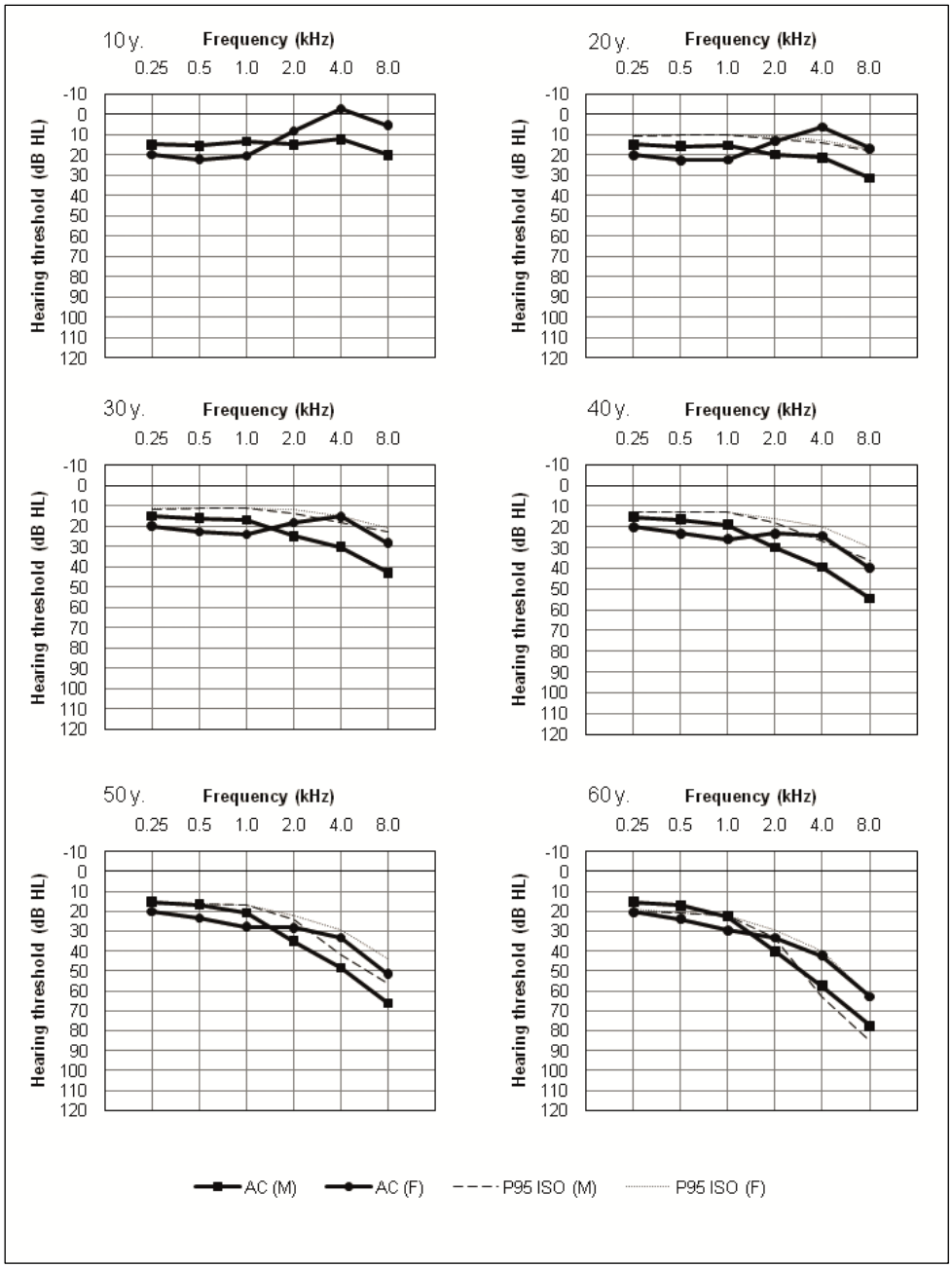

Figure 3. Age-related thresholds audiograms for osteogenesis imperfecta patients with pure sensorineural hearing loss

Six different audiograms represent the average air conduction (AC) thresholds in female (F) and male (M) osteogenesis imperfecta patients affected by pure sensorineural hearing loss at ages 10, 20, 30, 40, 50 and 60 years. Age-related air conduction thresholds corresponding to the 95th percentile in the healthy adult female [P95 ISO (F)] and male [P95 ISO (M)] population are indicated on the audiograms.

3.3. Speech audiometry

The SRT fitted into the expected 10-dB range around the PTA calculated from AC thresholds at 0.5, 1.0 and 2.0 kHz in 86.0% of the hearing-impaired ears. An SRT surpassing this PTA by more than 10 dB was recorded in 21.2% of the ears with a conductive/mixed and in 9.4% of those with a pure sensorineural hearing loss.

3.4. Acoustic admittance measurements

The tympanometric shape obtained at 226 Hz did not correspond to the type of the hearing loss, because tympanograms of types A, A_s and A_d tympanograms were registered to the same proportions in ears with normal, conductive, mixed, and sensorineural hearing loss (Table 2). Neither static acoustic admittance values nor the observation of type A_d tympanograms were associated with thin, translucent eardrums at micro-otoscopy. In ears with translucent eardrums, we found type A (77.8%) as well as A_d (13.0%) and A_s (9.3%) tympanograms.

Table 2. Tympanometric shapes (226 Hz) with regard to the hearing loss type.

Tympanometric shape	**Normal**	**Conductive/mixed hearing loss**	**Pure sensorineural hearing loss**
	(n=189)	***(n=65)***	***(n=42)***
Type A, No. of ears (%)	143 (75.7)	43 (66.2)	30 (71.4)
Type As, No. of ears (%)	24 (12.7)	10 (15.4)	6 (14.3)
Type Ad, No. of ears (%)	22 (11.6)	12 (18.4)	6 (14.3)

Terminology of the tympanometric shapes corresponds to the classification proposed by Jerger (1970)[26]

Two-component admittance measurements yielded normal results in 93.3% of ears with normal hearing, in 90.4% of ears with a conductive hearing loss component, and in 91.7% of the ears with a pure sensorineural loss.

3.5. ASR measurements

Ipsilateral and contralateral ASRs were elicitable at each of the four stimuli in 79.4% and in 67.7%, respectively, of the ears demonstrating normal hearing, whereas ipsilateral and contralateral ASRs were completely absent in all ears with conductive and mixed hearing losses. In the ears with pure sensorineural loss, ipsilateral and contralateral ASRs were absent in 40.5% and 45.2%, respectively. All normal-hearing ears with totally absent ASRs belonged to patients younger than 30 years.

4. Discussion

A considerable proportion of OI patients develop hearing loss, which manifests most often bilaterally and affects male and female patients to the same proportion. It may be either a conductive hearing loss that evolves to a mixed hearing loss, or a pure sensorineural hearing loss. Compared to pure sensorineural loss, conductive/mixed hearing loss in OI is more prevalent and is characterized by an

earlier onset and more severe progression. The age-related typical audiograms for both hearing loss types reflect these differences and may serve as a useful reference tool for otologists encountering patients with OI.

Although the prevalence of hearing loss may be influenced by a selection bias in favor of hearing loss, our overall 52.2% prevalence of hearing loss in OI largely agrees with those stated in other population studies[5-7, 11, 30] and family studies[8, 9, 31-35] investigating hearing in OI. However, the prevalence of hearing impairment in the OI population strongly depends on age. In the age range younger than 30 years, less than half of the patients demonstrate hearing loss, whereas 75% of the OI patients in the age range 30 to 39 years are hearing-impaired. In subsequent decades, little increase in the prevalence of hearing loss is expected. The risk that a patient with OI, demonstrating normal hearing at age 40 years, will develop hearing loss in the course of the following decades is very small. Nevertheless, in the hearing-impaired patients the thresholds progress to a more severe hearing loss. An association between increasing age and a growing proportion of hearing impairment in the OI population was already established by Riedner et al.[8], Pedersen[5], Stewart & O'Reilly[7] and Garretsen et al.[10] However, these studies report a continuing increase in the proportion of hearing-impaired patients after the fourth decade, attaining almost 100% in the age group above 60 years[5, 8, 10]. Except for the study by Pedersen[5], the sample size of OI patients in the older age groups were smaller in comparison with the present study. In addition, it is not clear whether the physiological age-related decline in hearing thresholds was taken into consideration in the studies by Riedner et al.[8], Pedersen[5] and Stewart & O'Reilly[7]. These methodological discrepancies possibly have led to overestimation of the hearing loss prevalence in the older OI population by previous studies.

More agreement between the present and earlier studies exists with regard to the type and onset of hearing deterioration in OI. Usually, a mild conductive hearing loss arises in the second to fourth decades of life and progresses to a moderate-to-severe mixed hearing loss in the following decades. In a few cases it will end up in profound hearing loss or deafness.[5-10, 12] Stapes footplate fixation is the most common cause for the OI-related conductive hearing loss and may be solved by stapes surgery. Though, compared to otosclerosis, such an intervention is more challenging in OI because of a higher risk on complications, such as extremely thick and hard, overgrown or brittle footplates, bleeding tendency of the highly vascularized middle ear mucosa and ossicular atrophy or fractures[13-17]. Therefore, differential diagnosis between both diseases is important. Subtle differences in the

audiometric patterns may assist in distuinguishing OI-related hearing loss from otosclerosis. Our ARTAs for OI patients with conductive/mixed hearing loss reflect progression of both the AC and BC thresholds, while the ABG remains relatively stable. Consequently, in OI, the hearing deterioration is mainly determined by progression of the sensorineural component, whereas otosclerosis is characterized by a progressive ABG but rarely by such a progressive sensorineural component. The ABG in OI appears to be age-independent, but frequency-specific as it is more prominent at the lower octave frequencies (≤1.0 kHz). The more severe hearing loss progression in OI and the more extensive inner ear involvement might be attributed to the overall inferior bone quality inherent to the disease, which renders the otic capsule more susceptible to become occupied by the continuing abnormal bone remodeling process that initially only affects the stapes footplate. Furthermore, in comparison with otosclerosis, the conductive hearing loss in OI has a relatively early onset, most often situated at the end of the second or the beginning of the third decade, whereas Nager[36] reported a mean age of 33 years for the development of otosclerosis. Finally, the OI-related conductive/mixed hearing loss is not characterized by a preponderance of female over male patients as is found in otosclerosis.

Shapiro et al.[34] introduced a mild high-frequency pure sensorineural hearing loss as the characteristic hearing loss in OI, affecting approximately 47% of OI patients. On the other hand, this so-called characteristic high-frequency sensorineural loss was observed only sporadically in other OI populations[5, 10, 12], as well as in ours, yielding a 1.4% prevalence of this isolated high-frequency pure sensorineural loss. More often, we observed a pure sensorineural loss involving the lower frequencies as well, affecting OI patients from all age categories, which is concordant with the findings of other large population studies[5-7, 10]. Compared with the above-described conductive/mixed hearing loss, this pure sensorineural loss in OI seems to be characterized by a slower progression with less severely affected thresholds. Separate ARTAs are constructed for OI patients developing this type of hearing loss, which confirm Pedersen's[5] impression that pure sensorineural hearing loss in OI parallels the normal physiologic deterioration in hearing ability with advancing age; however, the deterioration runs ahead in time. The ATD is smaller than 0.1 dB/year at octave frequencies below 1.0 kHz, but attains 1.0 and 1.2 dB/year at 4.0 and 8.0 kHz, respectively. Conspicuously, the ARTAs for female OI patients in their first 3 decades reflect low-frequent pure sensorineural loss, whereas thresholds at 4.0 and 8.0 kHz are within the 95th percentile of gender- and age-related thresholds in the healthy population.

Misdiagnosis of an initiating conductive loss as pure sensorineural hearing loss because of an initially subtle ABG but abnormally elevated average AC thresholds may probably explain this unexpected audiometric pattern of low-frequent sensorineural hearing loss in the young female OI population. Even admittance or stapedius reflex measurements cannot adequately identify a conductive component in the ears of OI patients. These audiologic tests have been assumed to be valuable for identification of middle ear pathologies and for differentiation between ossicular discontinuity and stapes fixation[37], two conditions that may contribute to hearing loss in OI. However, the translucent and hypermobile eardrums, typical for OI ears, apparently have a masking effect on the high and low admittance pathologies in the middle ear. Even when a high probe-tone is used, it remains difficult to interpret the results in light of the audiometric thresholds. Consequently, normal admittance and abnormally high or low admittance are recorded without any reference to the presence or type of hearing loss determined by pure-tone audiometry, which is consistent with earlier studies[7-9, 32, 34]. Biphasic acoustic reflexes, as an indicator of early stapes fixation were observed in OI ears by Riedner et al.[8] and Pedersen[5], but not in the present study, neither in those by Carruth et al.[32] and Cox & Simmons[9]. Furthermore, acoustic reflexes in OI patients with normal hearing thresholds may be absent, which also was noted in other studies with OI patients[5, 9, 12, 34]. Their absence might be an indicator of early stapedial fixation and a motivation for regular follow-up. Therefore, it is recommended to record ASRs in all OI patients and to bear in mind the risk of an initiating conductive loss in those patients with absent reflexes but normal audiograms.

Comparing the ARTAs for conductive/mixed hearing loss with those for pure sensorineural loss in OI yields differences in progression, severity, and audiometric configuration between both hearing loss types. The age-related BC thresholds of the mixed hearing loss type exceed the thresholds of the pure sensorineural losses from 40 years onwards, implying a more destructive inner ear pathology in the OI patients with mixed hearing loss compared with those with pure sensorineural loss. Consistent with other research[5, 34] we obtained well-preserved SRTs in OI-related hearing loss despite the relatively high prevalence of a sensorineural component. However, discrepancies between the audiometric AC thresholds and the SRT were observed more often in the OI patients with conductive/mixed than in those with pure sensorineural loss. In the OI patients demonstrating mixed hearing loss, the sensorineural component is most likely due to involvement of inner ear structures and pericochlear bone in the pathological bone remodeling process, whereas it initially only affects the stapes footplate

and causes a pure conductive hearing loss. More uncertainty remains about the pathophysiology of the pure sensorineural hearing loss in OI. It has been attributed to retrocochlear otosclerosis-like pathology, to hair cell atrophy, atrophy of the stria vascularis and microfractures of the cochlea. The presently depicted differences in audiologic characteristics assume a different underlying pathophysiology for both types of hearing loss in OI.

5. Conclusion

In the OI population, the prevalence of hearing loss is markedly elevated compared to the healthy population. Most often, a conductive hearing loss arises in the second to fourth decades of life and, thereafter, evolves to a mixed hearing loss characterized by an ATD of approximately 0.5 dB/year at low and mid-freqencies and 0.8 dB/year at the highest octave frequencies. After the age of 40 years, the risk to develop a hearing loss in OI is apparently reduced. However, a minority of OI patients develop a pure sensorineural hearing loss, which may initiate at any age. The latter hearing loss type is, in general, less progressive and less severe than the OI-related conductive or mixed hearing loss. Age-related typical audiograms for both types of hearing loss are established and may help the clinician to predict the course of the hearing loss in patients with OI. In addition, they may useful in the differential diagnosis between OI and otosclerosis, which is important when stapes surgery is considered. Regular follow-up of hearing in OI patients is recommended from a young age onwards, because the hearing loss often develops at school age and may severely interfere with learning skills when it remains undiagnosed.

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